In Silico Investigation of Some Glucose-Aspirin as COX Inhibitor

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Abstract

Monosaccharide derived glucose-aspirin (GA) can be prepared by conjugation between glucose and aspirin (ASA). The GA is reported to show higher analgesic and anti-inflammatory properties than ASA itself. In this perspective, six GAs which are composed of β-D-glucopyranose, ASA and acetyl groups are considered for the present investigations. The glucose unit in these GAs possesses regular chair conformation with slightly lower dipole moments. Molecular orbitals indicated a higher HOMO-LUMO gap of the molecules. All GAs showed more prone to electrophilic interactions than aspirin. Overall, glucose-aspirin esters are found to have better non-steroidal anti-inflammatory properties than the original aspirin. These GAs are better inhibitors of cyclooxygenase-2 (COX2, 5f19) compared to cyclooxygenase-1 (COX1, 6y3c) indicating that these GAs are potential drug candidates for COX2 related inflammation. Additionally, aspirinyl group at C-6 or C-3 position of the glucopyranose unit is found more suitable for anti-inflammatory activities as compared to C-4 position.

Keywords: *Anti-inflammatory drug, Cyclooxygenase (COX), Aspirin, Molecular docking, Sugar esters.*

1. Introduction

A common non-steroidal anti-inflammatory drug (NSAID) named aspirin (acetylsalicylic acid; ASA) is popular as a safe pain reliever [1]. It has been used for more than one hundred years. ASA has been used as antipyretic, analgesic, anti-inflammatory, antirheumatic, and antithrombotic drug [2-3]. It is used under several conditions such as headaches, toothaches, common cold, thromboembolic pulmonary hypertension, Felty's Syndrome, Reiter's syndrome, muscle pain, and peripheral artery disease. Among various advantages the most important is its use as primary and secondary prevention of cardiovascular diseases [4-5]. In fact, ASA can prevent myocardial attack and stroke. It was reported that around 55% of the elder people (>65 years) in USA are taking ASA daily or every other day [6]. In 1971 the exact pharmacological action mechanism of aspirin's was discussed which is mentioned as irreversible cyclooxygenase (COX) inhibition [7]. In addition, suppression of

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prostaglandin production along with COX inhibition was mentioned [8]. Many studies revealed that its COX inhibition action is due to the transfer of the acetyl group to the COX enzyme [9]. In other words, ASA acts as an acetylating agent to the COX (attached covalently with Ser529 of COX) and hence inactivates COX [8-9]. All these studies added value to the aspirin's proper use, measure, and evidence-based education.

However, ASA has several side effects due to its uneventful frequent use i.e. misuse. General adverse effects are vomiting, nausea, excess stomach acid secretion, heartburn, and intestine irritation [10]. All of these may trigger kidney and liver diseases, seasonal allergies, gastrointestinal upset, ulcers and bleeding [11-12]. These adverse effects (toxicity) led to a mild controversy about its use, dosage or need for further modifications. It was observed that the attachment of the glucose unit with aspirin produces a more water-soluble aspirin analogue called glucose-aspirin (GA) [13]. The GA was found more stable with significant analgesic and anti-inflammatory activities [13-14]. The sugar part i.e. glucose part generally contributes to increased water solubility [15-20], biodegradability [21-23] and bioactivities [24-29] of the attached remaining part(s). For example, the addition of monosaccharide units as in amphotericin and/or nystatin increases their bioactivity and reduces their side effects [30]. The esters of different monosaccharides were also found to possess higher antimicrobial functionality [31-36]. With sugar moiety, GA also exhibited significant anti-cancer activity under *in vitro* conditions [13].

Very little literature is available on glucose-aspirin (GA) although it's a superior potentiality to the aspirin (ASA) [13,14,37]. In principle, quantum chemical predictions are able to describe interactions between the molecule and biological receptors. Thus, in the present study six glucose-aspirins (GAs) are considered for thermodynamic and orbital properties, PASS analysis and molecular docking with COX enzyme.

2. Materials and methods

2.1. Glucose-aspirins (GAs) as COX inhibitors

In the present study, six glucose aspirins (Figure 1) are used mainly for the cyclooxygenase inhibitory activity study.

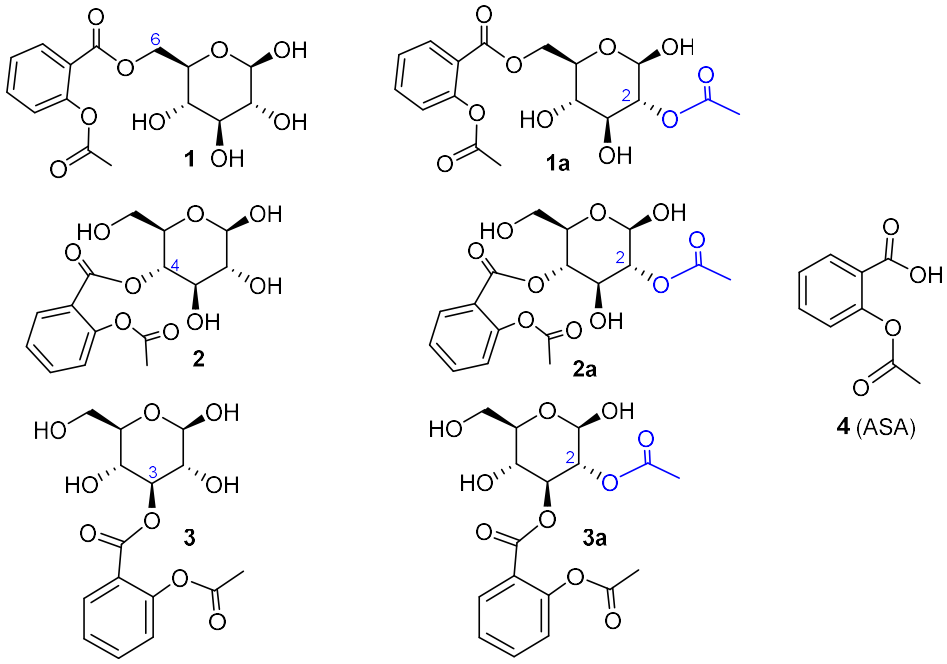

Figure 1. Glucose-aspirin (GA) compounds **1**-**3** and aspirin (**4**).

As a sugar unit β-D-glucopyranose is used. With this glucose unit, aspirinoyl group is shown to attach at C-6 (**1**), C-4 (**2**) and C-3 (**3**). Some of these compounds were synthesized by Jacob *et al*. [13-14]. For insight study of acetyl group here, acetyl group is also separately considered at C-2 position (**1a**-**3a**) in addition to the aspirinoyl unit. For comparative study aspirin (ASA, **4**) is also used.

2.2. DFT based optimization

Online Chemspider was used to collect proper β-D-glucose geometry [38-39]. The aspirin unit was then added to this β-D-glucose at C-6, C-4 or C-3 position in GaussView software [40] to get different GAs (**1**-**3**). In addition, the acetyl group was added to get **1a**-**3a**. For optimization of the GAs DFT (density functional theory) theory was used maintaining B3LYP method (6-31G+ basis set) in absence of solvent. It should be noted that for the inclusion of polarizable function 6-31G+ basis set was used. Optimized structures **1**-**3** and **1a**-**3a** were used for docking with COX enzyme.

2.3. Thermodynamic properties, molecular orbitals and chemical reactivity calculation

The optimized structures were used for several thermodynamic properties prediction employing GaussView and WebMD [23]. Molecular orbitals like HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) possess salient features for their inherent reactivity. As an example, the HOMO of a drug molecule is generally related to its electron releasing ability. Optimized structures were opened in GaussView software. Then values of HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) values were calculated and converted into electron Volt. These values were further used to calculate their chemical reactivity descriptors using literature equations [41-43]. For example, chemical potential (μ) = -(I+A)/2, where I = ionization potential and A = electron affinity.

2.4. PASS predication of glucose-aspirins

To predict and compare the aspirin related activities such as non-steroidal anti-inflammatory, antipyretic and anti-inflammatory properties we have employed predication of activity spectrum for substances (PASS) which is freely available after registration [44-45].

2.5. Method for molecular docking

Initially, the standard structure of aspirin in the SDF form was taken from ChemSpider. This compound and optimized glucose-aspirins are used as a ligand for docking studies. COX protein was taken from free online software named RCSB protein data bank (COX1 PDB id: 6y3c, and COX2 PDB id: 5f19). As the crystal structures possess water and hetero atoms the proteins were subjected to dehydration and hetero atoms removal followed by saving the file in PDB format. In the next step, the pdb file was energetically minimized in another software called Swisspdb.

For molecular docking, we mainly used PyRx autodock vina where ligands (compounds) and proteins (COX) are loaded duly. After minimization of their energy, they are converted into the necessary pdbqt file format. Before starting docking, the box sizes are maximized for autodock process and docked complex was opened with DiscoveryStudio for further study. Additionally, different interactions like nonbonding and hydrogen-bonding interactions among different GAs (ligands) and different amino acid residues of receptor protein(s) and binding affinities of ligand-protease were noted in the kcal/mole unit.

3. Results and discussion

3.1. Optimized structures of glucose-aspirins (GAs)

As in many of our studies, we emphasized conformational structures of carbohydrate part(s) of the compound(s), which may be interesting for activity studies [46-48]. In the case of GAs, the β-D-glucopyranosyl unit was found to exist in regular chair form with suitable $^4C_1$ conformation (Figure 2).

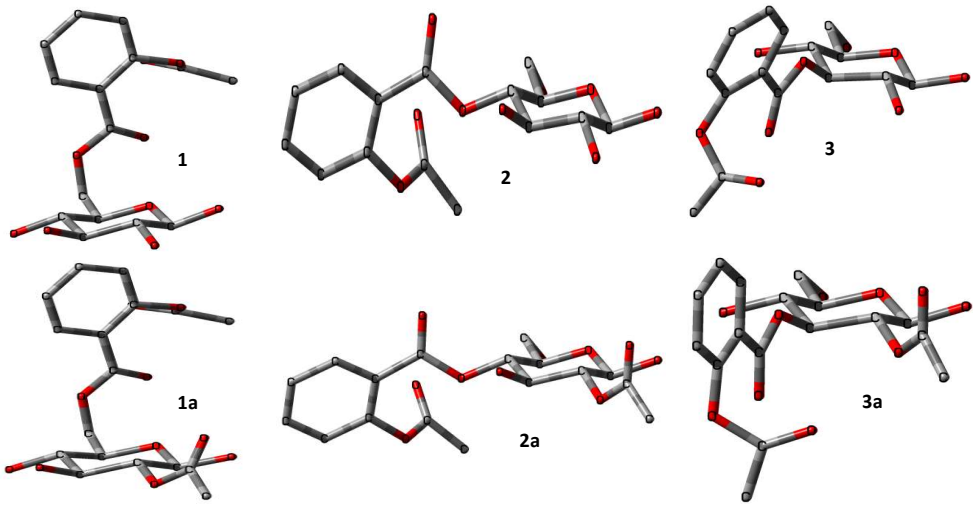

Figure 2. Structures of glucose-aspirins after DFT optimization (H atoms are not shown).

3.2. Thermodynamic studies

For comparison with aspirin, several thermodynamic properties are calculated from their DFT optimized files [49]. Table 1 indicated that due to the larger molecular size of glucose-aspirins (GAs) their electronic energy, Gibb's free energy (GFE), enthalpy and entropy are higher than aspirin. However, due to positional effects of aspirin part in GAs variable dipole moments are found for these GAs and thereby the position of aspirin group with glucose unit imposes variable polar nature of GAs. It has been reported that in many bioactive molecules there is a correlation between dipole moment and medicinal property [50]. Generally, a higher dipole moment is favourable for medicinal application as that compound is more soluble in a polar solvent. It is noticed from Table 1 that although **1a** (5.91 Debye) and **2a** (6.11 Debye) possess greater dipole moments **3a** (3.56 Debye) has a lower dipole moment. The greater dipole moment also indicates their higher mp/bp and solubility.

Table 1. Thermodynamic related properties of glucose-aspirins.

Molecule	Electronic energy (Hartree)	GFE (Hartree)	Enthalpy (Hartree)	Entropy (cal/mol-K)	Dipole moment (Debye)
1	-1259.1082	-1258.8353	-1258.7559	167.075	3.3264
1a	-1411.7203	-1411.4164	-1411.3268	188.474	5.9081
2	-1259.0992	-1258.8256	-1258.7473	164.795	3.1867
2a	-1411.7097	-1411.4052	-1411.3168	186.121	6.1119
3	-1259.0970	-1258.8260	-1258.7454	169.435	4.2439
3a	-1411.7143	-1411.4094	-1411.3214	185.200	3.5588
4	-649.6853	-649.5469	-649.4926	114.258	6.2099

3.3. Molecular orbitals and MEP of glucose-aspirins

To rationalize COX inhibitory activities and related results orbital properties of all the compounds were assessed as tabulated in Table 2. Here, hardness (η) is calculated as (I-A)/2 and softness (S) is equal to 1/η. HOMO-LUMO gap (Δε) of glucose-aspirins (GAs) is seen as higher than aspirin. However, the ionization potential (I), and chemical potential (μ) of both GAs and aspirin are almost similar (Table 2). Electron affinity (A) of **1**, **1a**, **2**, and **2a** are lower than the **3**, **3a** and **4**. The lower electron affinity indicates their better stability. Again, the hardness of all the GAs is higher than aspirin and softness is lower than aspirin (**4**).

Table 2. Orbitals of glucose-aspirins and related properties.

Compd.	εLUMO	εHOMO	Δε	I	A	μ	η	S
1	-1.886	-7.216	5.330	7.216	1.886	-4.551	2.665	0.375
1a	-1.880	-7.189	5.309	7.189	1.880	-4.535	2.655	0.367
2	-1.885	-7.295	5.410	7.295	1.885	-4.590	2.705	0.370
2a	-1.928	-7.344	5.416	7.344	1.928	-4.636	2.708	0.370
3	-2.042	-7.333	5.291	7.333	2.042	-4.688	2.646	0.378
3a	-2.243	-7.437	5.194	7.437	2.243	-4.840	2.595	0.385
4	-2.201	-7.135	4.934	7.135	2.201	-4.668	2.467	0.405

LUMO, HOMO, I, A, μ, η and S are expressed in eV.

Map process by molecular electrostatic potential (MEP) recognize one molecule from another in terms of biological interaction sites, receptor drugs and substrates like enzymes. MEP of all the compounds is presented in Figure 3.

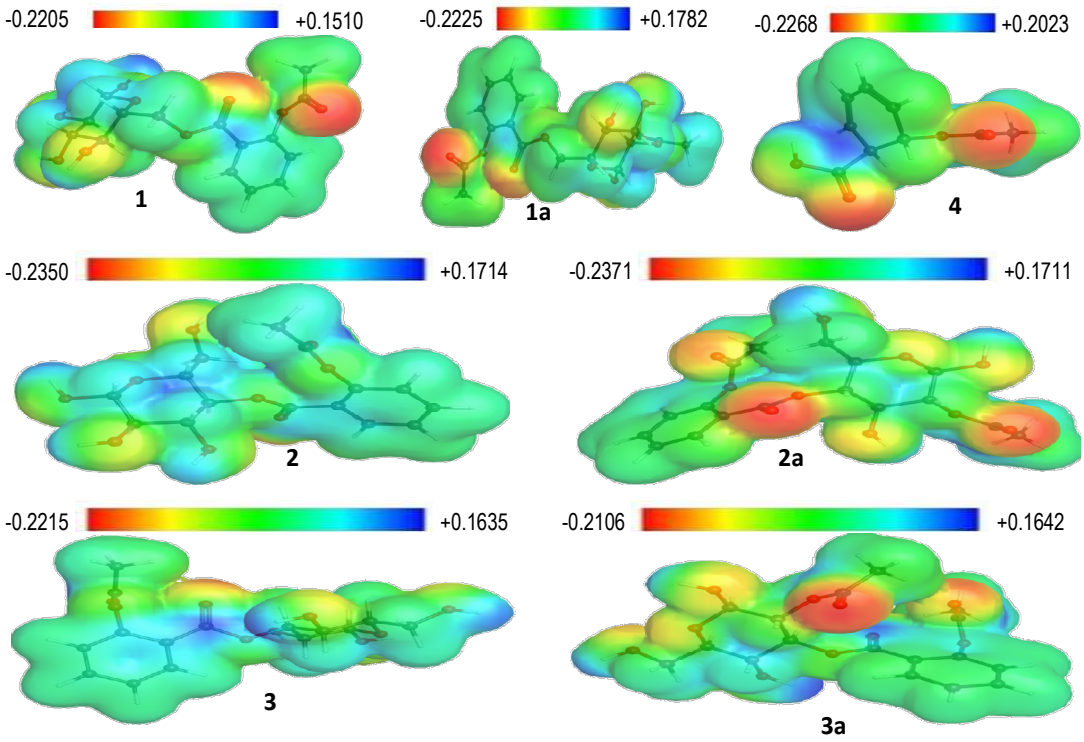

Figure 3. MEP of glucose-aspirins (**1**-**3** and **1a**-**3a**) and aspirin (**4**).

Generally, MEP is represented by the colour of the surface of the molecule depending on the potential values. MEP can be determined by diffraction technique in the laboratory and can be predicted by a computational method. It should be noted that the red colour represents the highest area for electrophilic reaction and the blue colour represent the highest area for nucleophilic interaction. The red zone for **1**-**3** and **1a**-**3a** are comparable to the aspirin (**4**).

The higher red zone of GAs **2** and **2a** indicate their higher electrophilic nature than aspirin i.e. 4-*O*-aspirinoylglucose possess better electrophilic nature than 6-*O*-aspirinoylglucose (**1**, **1a**) and 3-*O*-aspirinoylglucose (**3**, **3a**). Again, attachment of glucose unit with aspirin in any position decreases their nuceophilicity (Figure 3). It was reported that carbonyl oxygen atoms contribute red-coloured negative potential and carbonyl carbon and hydrogen atoms contribute blue coloured positive potential [51]. A similar observation is found in the present study (Figure 3).

3.4. PASS predicted NSAID, antipyretic and anti-inflammatory properties

Aspirin related three bioactivities as non-steroidal anti-inflammatory, antipyretic and anti-inflammatory properties are predicted using PASS free software. These predicted values are presented in Table 2. All the glucose-aspirins (GAs) (except **3a**) possess greater Pa (0.60-0.69) than the aspirin (0.55) indicating better non-steroidal nature of the GAs. Again, without acetyl group at C-2 position (**1a**-**3a**) of the glucose unit reduces the non-steroidal nature of the GAs (**1**-**3**, Table 2). Similarly, antipyretic potentiality of GAs (**1**-**3**) was also reduced with the introduction of acetyl group at the same position (**1a**-**3a**). The antipyretic property of GAs is lower than that of the aspirin. The anti-inflammatory effects of 6-*O*-asperinoylglucose (**1**, Pa = 0.78) and 4-*O*-asperinoylglucose (**2**, Pa = 0.77) are seen to be superior to the traditional aspirin (**4**, Pa = 0.76). Addition of acetyl part at C-2 (**1a**-**2a**) reduces anti-inflammatory effects than non-acetate (**1**-**2**) except **3a**. Overall, glucose-aspirin esters are found to have better non-steroidal anti-inflammatory properties than the original aspirin. Also,

these activities depend on the position of aspirin moiety in GAs and the order is found as C-6 > C-4 > C-3.

Table 2. NSAID and other activities predicted by PASS.

Molecule	NSAID agent		Antipyretic		Anti-inflammatory	
	Pa	Pi	Pa	Pi	Pa	Pi
1	0.687	0.005	0.644	0.005	0.776	0.008
1a	0.565	0.009	0.544	0.009	0.751	0.010
2	0.682	0.005	0.718	0.004	0.773	0.009
2a	0.558	0.009	0.633	0.005	0.749	0.010
3	0.606	0.007	0.764	0.009	0.724	0.004
3a	0.474	0.014	0.644	0.005	0.739	0.011
4	0.550	0.010	0.932	0.003	0.762	0.009

NSAID = Non-steroidal anti-inflammatory

3.5. Molecular docking: Binding affinity with COX

As aspirin and glucose-aspirins (GAs) are reported to possess anti-inflammatory and antipyretic properties (like other NSAID) two related proteins are considered for molecular docking. These are cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2). As presented in Table 3, the addition of aspirinyl group at C-6 (as in **1** and **1a**) and C-3 (as in **3** and **3a**) position of β-D-glucopyranose unit increased GA's binding potentiality with both the COX1 and COX2, while the addition of aspirinyl group at C-4 (as in **2** and **2a**) decreased binding score compared to GA **1**. In addition, GAs (**1**, **3**; -7.9 to -8.3 kcal/mol) and their acetyl esters (**1a**, **3a**; -6.5 to -8.2 kcal/mol) showed better binding scores than that of the standard drug ibuprofen (-6.5 to -6.7 kcal/mol). The docking scores are very much higher than the highly prescribed drug aspirin (ASA, Table 3). The binding energies of **1a** and **3a** are nicely stabilized by different non-bonding interactions (Figure 4). Overall, the GAs and their acetyl esters are better active against COX2 (5f19) compared to COX1 (6y3c).

Table 3. Molecular docking score (binding energy) with COX1 and COX2.

Molecule	6y3c (kcal/mol)	5f19 (kcal/mol)
1	-7.9	-8.3
1a	-8.0	-8.1
2	-6.3	-7.6
2a	-6.6	-7.7
3	-6.5	-7.9
3a	-8.2	-8.2
4	-5.3	-5.8
Ibuprofen	-6.7	-6.5

*For rigorous validation ibuprofen is used for docking in addition to aspirin.

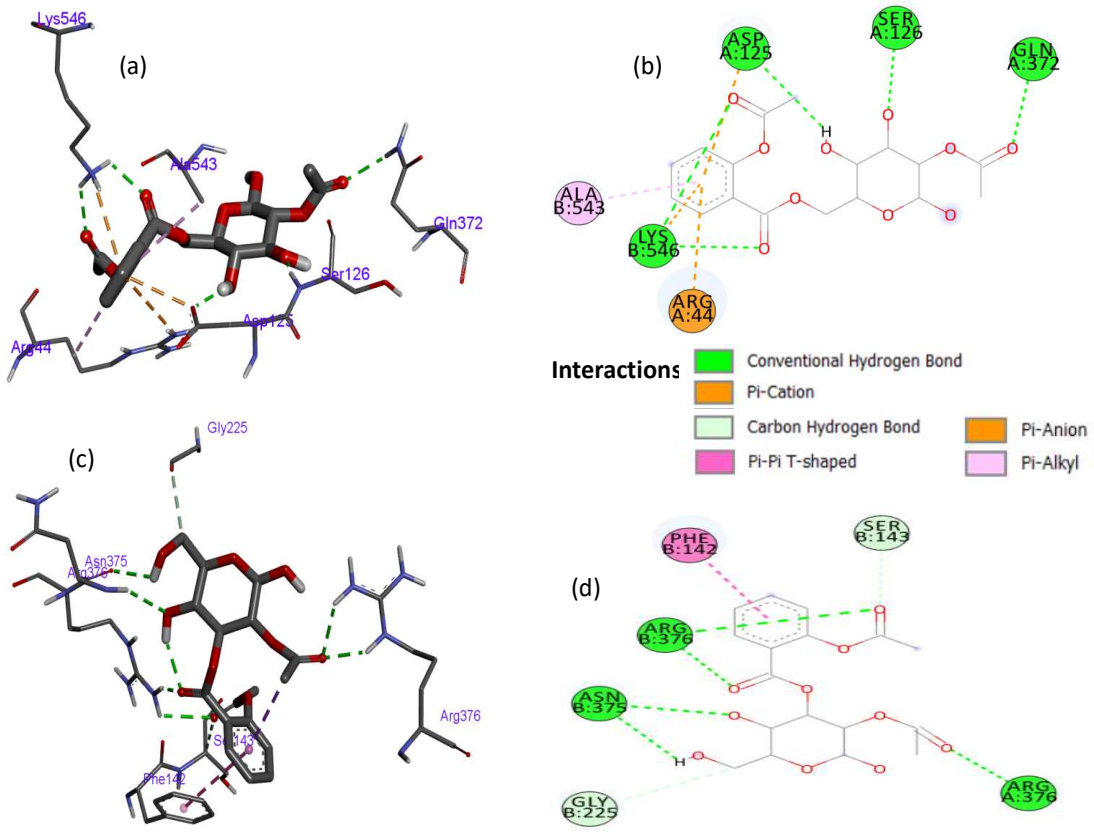

Figure 4. Different interactions (docking) of 5f19 with - (a) **1a** (3D); (b) **1a** (2D); (c) **3a** (3D); (d) **3a** (2D).

Interestingly, more active both the compounds **1a** and **3a** have higher electronic energy compared to **1**, **2** and **3** (Table 1). Also, they have higher Gibb's free energy and enthalpy. The docking results of GAs are found to be in agreement with the PASS predicted results as shown in Table 2.

4. Conclusion

Numerous superior anti-inflammatory and anticancer activities led us to design and *in silico* study six glucose-aspirins (GAs) as a non-steroidal anti-inflammatory drug (NSAID). The DFT oriented study indicated that all the GAs have regular chair conformation in their structures. Thermodynamically, their dipole moments are predicted lower than that of standard drugs namely aspirin (ASA). Molecular docking studies with cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) indicated that attachment of aspirinyl group at C-6 or C-3 position of glucopyranose unit is more suitable for anti-inflammatory activities as compared to C-4 position. The study also indicated that these GAs are potential drug candidates for COX2 related inflammation as compared to ibuprofen or aspirin.

References

[1] Flower, R. (2003). What are all the things that aspirin does? *British Medical Journal*, *327*, 572–573. https://doi.org/10.1136/bmj.327.7415.572

[2] Chen, H., Zhang, S. M., Hernan, M. A., Schwarzschild, M. A., Willett, W. C., Colditz, G. A., Speizer, F. E., & Ascherio, A. (2003). Non-steroidal anti-inflammatory drugs and the risk of Parkinson's disease. *Archives of Neurology*, *60*, 1059–1064. http://dx.doi.org/10.1001/archneur.60.8.1059

[3] Entminan, M., Sudeep, G., & Samii, A. (2003). Effect on non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *British Medical Journal*, *327*, 128–130. http://dx.doi.org/10.1136/bmj.327.7407.128

[4] Ittaman, S. V., VanWormer, J. J., & Rezkalla, S. H. (2014). The role of aspirin in the prevention of cardiovascular disease. *Clinical Medicine & Research*, *12*(3-4), 147–54. http://dx.doi.org/10.3121/cmr.2013.1197.

[5] Bartolucci, A. A., Tendera, M., Howard, G. (2011). Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *American Journal of Cardiology*, *107*, 1796–1801. http://dx.doi.org/10.1016/j.amjcard.2011.02.325

[6] Soni, A. (2013). Aspirin use among the adult U.S. non-institutionalized population, with and without indicators of heart disease, 2005. Statistical Brief #129. Agency for Healthcare Research and Quality, Medical Expenditure Panel Survey. Link: http://meps.ahrq.gov/mepsweb/data_files/publications/st179/stat179.pdf

[7] Vane, J. R., & Botting, R. M. (2003). The mechanism of action of aspirin. *Thrombosis Research*, *110*, 255-8. http://dx.doi.org/10.1016/s0049-3848(03)00379-7

[8] Mekaj, Y., Daci, F., & Mekaj, A. (2015). New insights into the mechanisms of action of aspirin and its use in the prevention and treatment of arterial and venous thromboembolism. *Therapeutics and Clinical Risk Management*, *11*, 1449-1456. https://doi.org/10.2147/TCRM.S92222

[9] Miner, J., & Hoffhines, A. (2007). The discovery of aspirin's antithrombotic effects. *Texas Heart Institute Journal*, *34*(2), 179–186.

[10] Krupski, W. C., Weiss, D. G., Rapp, J. H., Corson, J. D., Hobson, R. W. (1992). Adverse effects of aspirin in the treatment of asymptomatic carotid artery stenosis. *Journal of Vascular Surgery*, *16*(4), 588-600. https://doi.org/10.1016/0741-5214(92)90166-6

[11] Karsh, J. (1990). Adverse reactions and interactions with aspirin. Considerations in the treatment of the elderly patient. *Drug Safety*, *5*(5), 317-27. http://dx.doi.org/10.2165/00002018- 199005050-00002

[12] Weinberger, J. (2005). Adverse effects and drug interactions of antithrombotic agents used in prevention of ischaemic stroke. *Drugs*, *65*(4), 461-71. http://dx.doi.org/10.2165/00003495-200565040-00003

[13] Jacob, J. N., & Tazawa, M. J. (2012). Glucose–aspirin: Synthesis and in vitro anti-cancer activity studies. *Bioorganic & Medicinal Chemistry Letters*, *22*, 3168–3171. http://dx.doi.org/10.1016/j.bmcl.2012.03.053

[14] Jacob, J. N., Badyal, D. K. & Bala, S. (2013). Evaluation of the in vivo anti-inflammatory and analgesic activity of a highly water-soluble aspirin conjugate. *Basic & Clinical Pharmacology & Toxicology*, *112*, 171–174. http://dx.doi.org/10.1111/bcpt.12006

[15] Dhavale, D. D., Matin, M. M., Sharma, T., & Sabharwal, S. G. (2003). N-Hydroxyethyl-piperidine and –pyrrolidine homoazasugars: preparation and evaluation of glycosidase inhibitory activity. *Bioorganic & Medicinal Chemistry*, *11*(15), 3295–3305. https://doi.org/10.1016/S0968-0896(03)00231-1

[16] Dhavale, D. D., & Matin, M. M. (2004). Selective sulfonylation of 4-C-hyroxymethyl-β-L-threo-pento-1,4-furanose: Synthesis of bicyclic diazasugars. *Tetrahedron*, *60*(19), 4275–4281. https://doi.org/10.1016/j.tet.2004.03.034

[17] Muhammad, D., Matin, M. M., Miah, S. M. R., Devi, P. (2021). Synthesis, antimicrobial, and DFT studies of some benzyl 4-O-acyl-α-L-rhamnopyranosides. *Orbital: The Electronic Journal of Chemistry*, *13*(3), 250–258. http://dx.doi.org/10.17807/orbital.v13i3.1614

[18] Matin, M. M., Bhuiyan, M. M. H., Afrin, A., & Debnath, D. C. (2013). Comparative antimicrobial activities of some monosaccharide and disaccharide acetates. *Journal of Scientific Research*, *5*(3), 515–525. http://dx.doi.org/10.3329/jsr.v5i3.15695

[19] Kabir, A. K. M. S., Matin, M. M., Hossain, A., & Sattar, M. A. (2003). Synthesis and antimicrobial activities of some rhamnopyranoside derivatives. *Journal of the Bangladesh Chemical Society*, *16*(2), 85–93. ISSN: 1022-016X

[20] Matin, M. M. (2014). Synthesis and antimicrobial study of some methyl 4-*O*-palmitoyl-α-L-rhamnopyranoside derivatives. *Orbital: The Electronic Journal of Chemistry*, *6*(1), 20–28. https://doi.org/10.17807/orbital.v6i1.553

[21] Matin, M. M., Bhuiyan, M. M. H., Debnath, D. C., & Manchur, M. A. (2013). Synthesis and comparative antimicrobial studies of some acylated D-glucofuranose and D-glucopyranose derivatives. *International Journal of Biosciences*, *3(*8), 279–287. http://dx.doi.org/10.12692/ijb/3.8.279-287

[22] Kabir, A. K. M. S., & Matin, M. M. (1994). Regioselective acylation of a derivative of L-rhamonse using the dibutyltin oxide method. *Journal of the Bangladesh Chemical Society*, *7*(1), 73–79. ISSN: 1022-016X
[23] Ali, M., Karim, M. H., & Matin, M. M. (2021). Efficient synthetic technique, PASS predication, and ADMET studies of acylated n-octyl glucopyranosides. *Journal of Applied Science & Process Engineering*, *8*(1), 648–659. https://doi.org/10.33736/jaspe.2823.2021
[24] Kabir, A. K. M. S., Matin, M. M., Mridha, M. A. U., & Shahed, S. M. (1998). Antifungal activities of some methyl 6-*O*-trityl-α-D-mannopyranosides. *The Chittagong University Journal of Science*, *22*(1), 41–46. ISSN: 1561-1167
[25] Kabir, A. K. M. S., Matin, M. M., Sanaullah, A. F. M., Sattar, M. A., & Rahman, M. S. (2001). Antimicrobial activities of some lyxoside derivatives. *Bangladesh Journal of Microbiology*, *18*(1), 89–95. ISSN: 1011-9981
[26] Kabir, A. K. M. S., Matin, M. M., Bhuiyan, M. M. R., Rahim, M. A., Rahman, M. S. (2005). Biological evaluation of some monosaccharide derivatives. *International Journal of Agriculture and Biology*, *7*(2), 218–221. ISSN: 1560-8530
[27] Matin, M. M., & Iqbal, M. Z. (2021). Methyl 4-O-(2-chlorobenzoyl)-α-L-rhamnopyranosides: Synthesis, characterization, and thermodynamic studies. *Orbital: The Electronic Journal of Chemistry*, *13*(1), 19–27. http://dx.doi.org/10.17807/orbital.v13i1.1532
[28] Matin, M. M., Bhuiyan, M. M. H., Azad, A. K. M. S., Akther, N. (2017). Design and synthesis of benzyl 4-O-lauroyl-α-L-rhamnopyranoside derivatives as antimicrobial agents. *Current Chemistry Letters*, Vol.*6*, No.1, 31–40. https://doi.org/10.5267/j.ccl.2016.10.001
[29] Matin, M. M., & Ibrahim, M. (2010). Synthesis of some methyl 4-O-octanoyl-α-L-rhamnopyranoside derivatives. *Journal of Applied Sciences Research*, *6*(10), 1527–1532. ISSN: 1816-157X
[30] Kim, H. J., Kang, S. H., Choi, S. S., & Kim, E. S. (2017). Redesign of antifungal polyene glycosylation: engineered biosynthesis of disaccharide-modified NPP. *Applied Microbiology & Biotechnology*, *101*, 5131–5137. https://doi.org/10.1007/s00253-017-8303-8
[31] Matin, M. M., Bhuiyan, M. M. H., Azad, A. K. M. S., & Rashid, M. H. O. (2015). Synthesis of 6-O-stearoyl-1,2-O-isopropylidene-α-D-gluco-furanose derivatives for antimicrobial evaluation. *Journal of Physical Science*, *26*,(1), 1–12. ISSN: 1675-3402
[32] Zago, E., Joly, N., Chaveriat, L., Vincent Lequart, V., & Martin, P., (2021). Enzymatic synthesis of amphiphilic carbohydrate esters: Influence of physicochemical and biochemical parameters, *Biotechnology Reports*, *30*, e00631, https://doi.org/10.1016/j.btre.2021.e00631
[33] Matin, M. M., Bhuiyan, M. H., Hossain, M. M., & Roshid, M. H. O. (2015). Comparative antibacterial activities of some monosaccharide and disaccharide benzoates. *Orbital: The Electronic Journal of Chemistry*, *7*(2), 160–167. https://doi.org/10.17807/orbital.v7i2.699
[34] Matin, M. M. (2006). Synthesis of some silyl protected 1,4-galactonolactone derivatives. *Journal of Applied Sciences Research*, *2*(10), 753–756. ISSN: 1816-157X
[35] Chowdhury, A. Z. M. S., & Matin, M. M. (1997). Synthesis of imidazo[1,2-c]pyrido[4′,3′:4,5]thieno[3,2-e]-pyrimidine. *Chittagong University Studies, Part II: Science*, *21*(2), 47–52. ISSN: 0253-5459
[36] Khairulzaim, A. A. B. M., Rahman, M. R., Roslan, L., Bakri, M. K. B., Khan, A., Matin, M. M. (2021). Analysis of char prepared by pyrolysis of dabai (Canarium odontophyllum) nutshells as a potential precursor of biocarbon used for wastewater treatment. *BioResources*, *16(*3), 5036–5046. https://doi.org/10.15376/biores.16.3.5036-5046
[37] Santos, C. B. R., Lobato, C. C., Braga, F. S., Morais, S. S. S., Santos, C. F., Fernandes, C. P., Brasil, D. S. B., Hage-Melim, L. I. S., Macedo, W. J. C., & Carvalho, J. C. T. (2014). Application of Hartree-Fock method for modeling of bioactive molecules using SAR and QSPR, *Computational Molecular Bioscience*, *4*, 1–24. http://dx.doi.org/10.4236/cmb.2014.41001
[38] Matin, M. M., Uzzaman, M., Chowdhury, S. A., & Bhuiyan, M. M. H. (2020). In vitro antimicrobial, physicochemical, pharmacokinetics, and molecular docking studies of benzoyl uridine esters against SARS-CoV-2 main protease. *Journal of Biomolecular Structure and Dynamics*, 1-13. https://doi.org/10.1080/07391102.2020.1850358
[39] Matin, M. M., Hasan, M. S., Uzzaman, M., Bhuiyan, M. M. H., Kibria, S. M., Hossain, M. E., & Roshid, M. H. O. (2020). Synthesis, spectroscopic characterization, molecular docking, and ADMET studies of mannopyranoside esters as antimicrobial agents. *Journal of Molecular Structure*, *1222*, 128821. https://doi.org/10.1016/j.molstruc.2020.128821
[40] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., et al. (2013). Gaussian 09W, Revision D.01. Gaussian, Inc., Wallingford CT.

[41] Matin, M. M., Chakraborty, P., Alam M. S., Islam, M. M., & Hanee, U. (2020) Novel mannopyranoside esters as sterol 14α-demethylase inhibitors: Synthesis, PASS predication, molecular docking, and pharmacokinetic studies. *Carbohydrate Research*, *496*, 108130. https://doi.org/10.1016/j.carres.2020.108130

[42] Pehkonen, S. O., & Yuan, S. (2018). Chapter 1 - Introduction and Background. *Interface Science and Technology*, *23*, 1-11. https://doi.org/10.1016/B978-0-12-813584-6.00001-6

[43] Matin, M. M., Bhuiyan, M. M. H., Kabir, E., Sanaullah, A. F. M., Rahman, M. A., Hossain, M. E., & Uzzaman, M. (2019). Synthesis, characterization, ADMET, PASS predication, and antimicrobial study of 6-O-lauroyl mannopyranosides. *Journal of Molecular Structure*, *1195*, 189–197. https://doi.org/10.1016/j.molstruc.2019.05.102

[44] Filimonov, D.,A., Lagunin, A. A., Gloriozova, T. A., Rudik, A. V., Druzhilovskii, D. S., Pogodin, P. V., Poroikov, V. V. (2014). Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chemistry of Heterocyclic Compounds*, *50(3)*, 444–457. https://doi.org/10.1007/s10593-014-1496-1

[45] Matin, M. M., Bhattacharjee, S. C., Chakraborty, P., & Alam M. S. (2019). Synthesis, PASS predication, in vitro antimicrobial evaluation and pharmacokinetic study of novel n-octyl glucopyranoside esters. *Carbohydrate Research*, *485*, 107812. https://doi.org/10.1016/j.carres.2019.107812

[46] Devi, P., Matin, M. M., Bhuiyan, M. M. H., & Hossain, M. E. (2021). Synthesis, and spectral characterization of 6-O-octanoyl-1,2-O-isopropylidene-α-D-glucofuranose derivatives. *Journal of the Turkish Chemical Society Section A: Chemistry*, *8*(4), 1003-1024. https://doi.org/10.18596/jotcsa.929996

[47] Bakri, M. K. B., Rahman, M. R., & Matin, M. M. (2021). Cellulose reinforcement in thermoset composites. In: Fundamentals and Recent Advances in Nanocomposites Based on Polymers and Nanocellulose, MR Rahman (Ed), 1st Ed, Elsevier Science, 127-142. https://doi.org/10.1016/B978-0-323-85771-0.00011-7

[48] Taib, N-. A. B., Rahman, M. R., Bakri, M. K. B., & Matin, M. M. (2021). Advanced techniques for characterizing cellulose. In: Fundamentals and Recent Advances in Nanocomposites Based on Polymers and Nanocellulose, MR Rahman (Ed), 1st Ed, Elsevier Science, 2021, 53-84. https://doi.org/10.1016/B978-0-323-85771-0.00001-4

[49] Islam, N., Islam, M. D., Rahman, M. R., & Matin, M. M. (2021). Octyl 6-O-hexanoyl-β-D-glucopyranosides: Synthesis, PASS, antibacterial, in silico ADMET, and DFT studies. *Current Chemistry Letters*, *10*(4), 413-426. https://doi.org/10.5267/j.ccl.2021.5.003

[50] Rahim, A., Bhuiyan, M. M. H., & Matin, M. M. (2020). Microwave assisted efficient synthesis of some flavones for antimicrobial and ADMET studies. *Journal of Scientific Research*, *12*(4), 673-685. http://dx.doi.org/10.3329/jsr.v12i4.45523

[51] Fraga, C. A. M. (2001). Razões da Atividade Biológica: Interações Micro- e Biomacromoléculas. *Química Nova na Escola*, São Paulo-SP, 33–42.